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Myocardial Perfusion and Sympathetic Innervation in Patients With Hypertrophic Cardiomyopathy

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OBJECTIVES This study assessed left ventricular myocardial perfusion and sympathetic innervation and function in hypertrophied and nonhypertrophied myocardial regions of patients with hypertrophic cardiomyopathy (HCM).

BACKGROUND Patients with HCM often have clinical findings consistent with increased cardiac sympathetic outflow. Little is known about the status of sympathetic innervation specifically in hypertrophic regions.

METHODS We conducted positron emission tomographic (PET) scanning using the perfusion imaging agent ^{13}N-ammonia ($^{13}NH_3$) and the sympathoneuronal imaging agent 6-[^{18}F]-fluorodopamine (^{18}F-FDA) in 8 patients with HCM and 15 normal volunteers. Positron emission tomographic data corrected for attenuation and the partial volume effect were analyzed using the region-of-interest technique.

RESULTS Myocardial $^{13}NH_3$-derived radioactivity was similar in hypertrophied and nonhypertrophied regions of patients with HCM and in normal volunteers. At all time points, the ^{18}F:^{13}N ratio was lower in hypertrophied than in nonhypertrophied regions of HCM patients and in the septum of normal volunteers ($p = 0.001$). Trends in ^{18}F-FDA-derived radioactivity over time were normal in both hypertrophied and nonhypertrophied myocardium.

CONCLUSIONS The results are consistent with decreased neuronal uptake of catecholamines in hypertrophied but not in nonhypertrophied myocardium of patients with HCM. Other aspects of cardiac sympathoneural function seem normal. Decreased neuronal uptake could reflect local relative hypoinnervation, decreased numbers of neuronal uptake sites, or metabolic limitations on cell membrane transport. By enhancing norepinephrine delivery to adrenoceptors for a given amount of sympathetic nerve traffic, decreased neuronal uptake can explain major clinical features of HCM. (J Am Coll Cardiol 2000;35:1867–73) © 2000 by the American College of Cardiology

Hypertrophic cardiomyopathy (HCM) is a genetic disease inherited as an autosomal dominant trait and characterized by left ventricular hypertrophy in the absence of other causes for increased cardiac mass (1–5). The disease results from missense mutations of genes encoding sarcomeric proteins such as beta-myosin heavy chain, essential and regulatory light chain of myosin, alpha-tropomyosin, cardiac troponin T or I, or cardiac myosin binding protein C (6–11).

Clinical features of HCM, such as chest pain, progression of left ventricular hypertrophy, myocardial hypercontractility, propensity to ventricular arrhythmias and sudden death, and the beneficial effect of beta-adrenoceptor blockers, suggest increased cardiac sympathetic outflow and, consequently, increased delivery of the sympathetic neurotransmitter, norepinephrine, to myocardial adrenoceptors (3–5,12,13). Norepinephrine not only elicits vasoconstriction, increases myocardial oxygen consumption, and increases the rate of spontaneous depolarization of myocardial cells acutely, but also acts as a hypertrophic factor in cardiovascular smooth muscle cells (14–17).

Any of several abnormalities of cardiac sympathetic innervation or function can increase norepinephrine delivery to adrenoceptors. The most straightforward is an increase in the rate of local sympathetic nerve traffic, which increases release of norepinephrine from the nerve terminals. Although a previous study reported an increased appearance rate of norepinephrine in plasma in the great cardiac vein (cardiac norepinephrine spillover) in patients with HCM (18), the increase was relatively small, and, as noted below, increased cardiac sympathetic traffic alone cannot account for some other neurochemical findings.

Decreased neuronal reuptake of norepinephrine (Uptake-1), the main means for terminating the actions of norepi-

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Abbreviations and Acronyms

$^{13}NH_3$	= ^{13}N-ammonia
^{18}F-FDA	= 6-[^{18}F]-fluorodopamine
HCM	= hypertrophic cardiomyopathy
PET	= positron emission tomography
ROI	= region of interest

nephrine in the human heart (19), also increases delivery of norepinephrine to adrenoceptors (20). Consistent with this mechanism, patients with HCM have a decreased fractional extraction of ^{3}H-norepinephrine and a decreased arteriovenous increment in plasma levels of dihydroxyphenylglycol, the main neuronal metabolite of norepinephrine, compared with control patients (18).

Studies of cardiac kinetics of ^{3}H-norepinephrine and its metabolites cannot provide information about possible abnormalities of sympathetic innervation or function specifically in hypertrophied regions. Investigators (21,22) have reported decreased ^{123}I-meta-iodozylganidine-derived (^{123}I-MIBG-derived) radioactivity in the hypertrophied regions of patients with HCM, and Schafers et al. (23) reported reduced ^{11}C-hydroxyephedrine-derived radioactivity. These findings are consistent with locally decreased Uptake-1 activity; however, other abnormalities of cardiac sympathetic function can produce the same results.

Positron emission tomographic (PET) scanning after injection of 6-[^{18}F]-fluorodopamine (^{18}F-FDA), a newly developed catecholamine that acts as a false adrenergic neurotransmitter (Fig. 1), can visualize cardiac sympathetic innervation and function (24–29). Sympathetic nerve terminals rapidly take up circulating ^{18}F-FDA and sequester it extensively in axoplasmic vesicles (24,30). The heart:blood ratio of ^{18}F-FDA is 2:1 at 5 min and 9:1 at 180 min after injection (27).

Alterations in specific aspects of sympathetic neuroeffector function, including Uptake-1 activity, vesicular transport and storage of monoamines, oxidative deamination, and postganglionic sympathetic nerve traffic, produce characteristic changes in curves relating ^{18}F-FDA–derived myocardial radioactivity to time (time-activity curves, TACs). Treatment with desipramine, which blocks Uptake-1, or 6-hydroxydopamine, which destroys sympathetic nerve terminals, decreases cardiac uptake of ^{18}F-FDA (25,27,31). Reserpine, which blocks vesicular transport of axoplasmic monoamines, does not affect myocardial uptake of ^{18}F-FDA but markedly decreases retention of ^{18}F-FDA (25). Increased sympathetic activity, induced by exercise or sublingual nitroglycerin, increases the rate of loss of ^{18}F-FDA–derived myocardial radioactivity (32), whereas ganglion blockade with trimethaphan prolongs the loss of ^{18}F-FDA–derived myocardial radioactivity (25,27).

This study used ^{18}F-FDA PET scanning to evaluate whether patients with HCM have alterations in sympathetic innervation or function in the hypertrophied regions that might predispose to a hyperadrenergic state. We also used the perfusion imaging agent ^{13}N-ammonia ($^{13}NH_3$) (33) to adjust ^{18}F-FDA concentrations for possible regional differences in delivery by the bloodstream (^{18}F:^{13}N ratio).

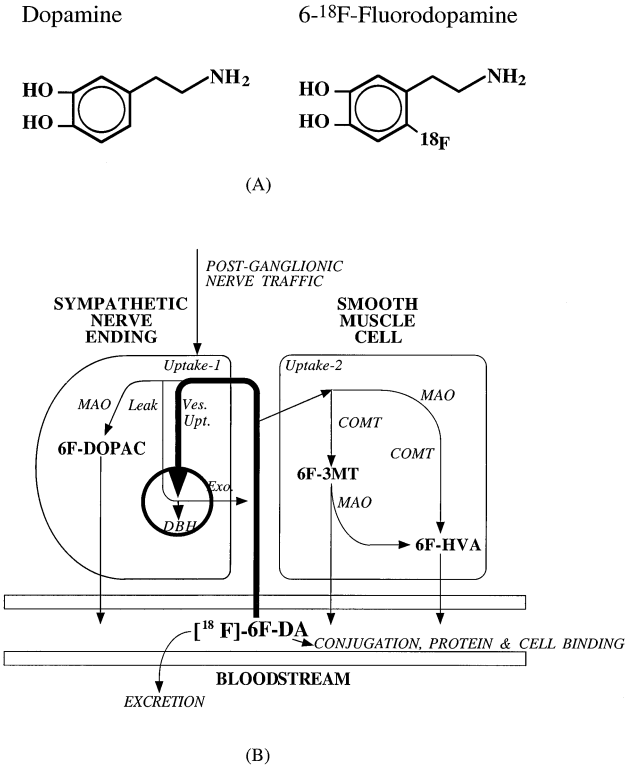

Figure 1. The structure **(A)** and fate of 6-[^{18}F]-fluorodopamine **(B).**

METHODS

Subjects. Both ^{18}F-FDA and $^{13}NH_3$ were administered and thoracic PET scanning performed in 15 healthy adult volunteers (11 men and 4 women, aged 54 ± 22 years) and 8 patients with HCM (6 men and 2 women, aged 42 ± 18 years). All the volunteers had normal medical history, physical examination, electrocardiogram (ECG), and laboratory (blood and urine) tests. Of the 8 HCM patients, asymmetric septal hypertrophy was present in 5 (2 with hypertrophy of the apex as well), whereas hypertrophy was more diffuse in 3 patients, so that there were 8 hypertrophied and 5 nonhypertrophied regions. Caffeine-containing beverages, cigarettes, and alcohol were proscribed for at least 24 h before PET scanning.

The study protocol was approved by the Clinical Research Subpanel of the National Institute of Neurological Disorders and Stroke (NINDS). Each subject gave written informed consent.

PET scanning. Three-dimensional PET studies were performed on an Advance™ whole-body scanner (General Electric, Milwaukee, Wisconsin). An 8-min transmission scan, using rotating ^{68}Ge/^{68}Ga pin sources, was obtained for

attenuation correction and for confirming the location of the heart, before the $^{13}NH_3$ and ^{18}F-FDA PET scans. Immediately after the first transmission scan, myocardial perfusion was assessed by PET imaging (35 contiguous transaxial slices 4.25 mm apart) for 20 min after a 1-min IV infusion of 5 mCi of $^{13}NH_3$.

For sympathoneuronal imaging, after the second transmission scan, PET images (35 contiguous transaxial slices 4.25 mm apart) were acquired after IV infusion of ^{18}F-FDA (synthesized as described previously) (27) at a constant rate for 3 min after, beginning at least 1 h after $^{13}NH_3$ administration. A series of PET scans (5 frames × 1 min, 5 × 5 min, 4 × 15 min, and 3 × 30 min, total 3 h) was acquired.

Data analysis. The ^{18}F-FDA data were reconstructed after correction for attenuation and for physical decay of ^{18}F. Cardiac images were analyzed as described previously (27). Briefly, circular regions of interest (ROIs) approximately half the ventricular wall thickness were placed on images of the septum, lateral wall, and left ventricular chamber using time-averaged pictures of a single slice. Left ventricular radioactivity was averaged from two ROIs each in the left ventricular free wall and septum. Time-activity curves relating myocardial radioactivity with time were constructed from the dynamic PET data and compared between the HCM and control groups.

Static $^{13}NH_3$ PET images were reconstructed after analogous correction for attenuation and physical decay of ^{13}N and analyzed using the same ROI technique.

Radioactivity concentrations were standardized by correcting for the dose of radioactive drug per unit body mass of the subject and expressed as nCi · kg/cc · mCi.

Because infused ^{18}F-FDA is delivered by the bloodstream, the amount of ^{18}F-FDA–derived radioactivity depends on regional perfusion. To correct ^{18}F-FDA–derived radioactivity for regional perfusion, the ratio of ^{18}F-FDA–derived radioactivity to $^{13}NH_3$-derived radioactivity (^{18}F:^{13}N) was calculated in the same ROIs.

Correction for partial volume effect. Because of asymmetric septal hypertrophy, increased septal myocardial concentrations of ^{18}F and ^{13}N might reflect a partial volume effect. To correct for this effect, thicknesses of the left ventricualr free wall and septum were measured by echocardiography, and recovered coefficient functions for the GE Advance™ PET scanner were calculated and applied by blurring in-plane data with a two-dimensional Gaussian filter (34,35).

Statistics. All data were expressed as means ± SEM. The HCM and normal volunteer groups were compared using between–within analyses of variance (2-factor repeated-measures analysis of variance [ANOVA]), the between factor being diagnosis and the within factor being time (StatView SE+Graphics™, Abacus Concepts, Berkeley, California). A factorial ANOVA was used to assess effects of blood flow and diagnostic group on myocardial ^{18}F-FDA–derived radioactivity.

Bi-exponential equations of best fit were calculated using a "peeling" approach to describe the relationships between myocardial radioactivity and time in each subject. The equation for the mono-exponential line of best fit for the late phase, including the y-intercept (y_o) and apparent rate constant (k), was determined for the last four scanning intervals (midpoints 97.5 min to 165 min after administration of ^{18}F-FDA; Cricket Software, Malvern, Pennsylvania). Differences between the estimated and empirical values were calculated and graphed, and the mono-exponential line of best fit for the early phase was determined, beginning with the peak value of ^{18}F-FDA–derived radioactivity. Values for y_o and k for the early phase were than calculated.

Values for y_o and k for ^{18}F-FDA–derived radioactivity, with and without adjustment for perfusion, were compared to those in the normal volunteers, using independent-means *t*-tests. Statistical significance was defined by a p value less than 0.05.

RESULTS

After administration of ^{18}F-FDA or $^{13}NH_3$, the left ventricular myocardium was visualized clearly in all subjects (Fig. 2). The myocardial distribution of both tracers was more heterogeneous in patients with HCM than in normal volunteers.

Mean left ventricular myocardial radioactivity. Values for time-averaged $^{13}NH_3$-derived radioactivity in left ventricular myocardium as a whole were similar in patients with HCM (7137 ± 506 nCi · kg/cc · mCi) and in normal volunteers (7293.4 ± 409 nCi · kg/cc · mCi; Fig. 3).

The mean concentration of ^{18}F-FDA–derived radioactivity in left ventricular myocardium increased to a peak at 5 to 8 min after initiation of the 3-min infusion in both subject groups (8499 ± 722 nCi · kg/cc · mCi in HCM patients, 10,263 ± 673 nCi · kg/cc · mCi in normal volunteers). The ^{18}F-FDA–derived radioactivity thereafter declined bi-exponentially. In both the early and late phases of the decline, the groups did not differ in mean values for k or y_o (Table 1).

There was a significant time-dependent decline of ^{18}F-FDA–derived radioactivity ($F = 134.2$, $p = 0.0001$). Patients with HCM had a lower mean ratio of ^{18}F:^{13}N than did the normal volunteers ($F = 11.1$, $p = 0.0039$), and the trend in ^{18}F:^{13}N differed significantly between the groups ($F = 2.39$, $p = 0.0085$; Fig. 4, upper part). The peak value also occurred significantly earlier in the HCM patients (5.1 min vs. 8.0 min; Fig. 4, lower part).

Hypertrophied versus nonhypertrophied regions in patients with HCM. After correction for the partial volume effect, mean $^{13}NH_3$-derived radioactivity in hypertrophied regions did not differ from that in nonhypertrophied regions (Fig. 3).

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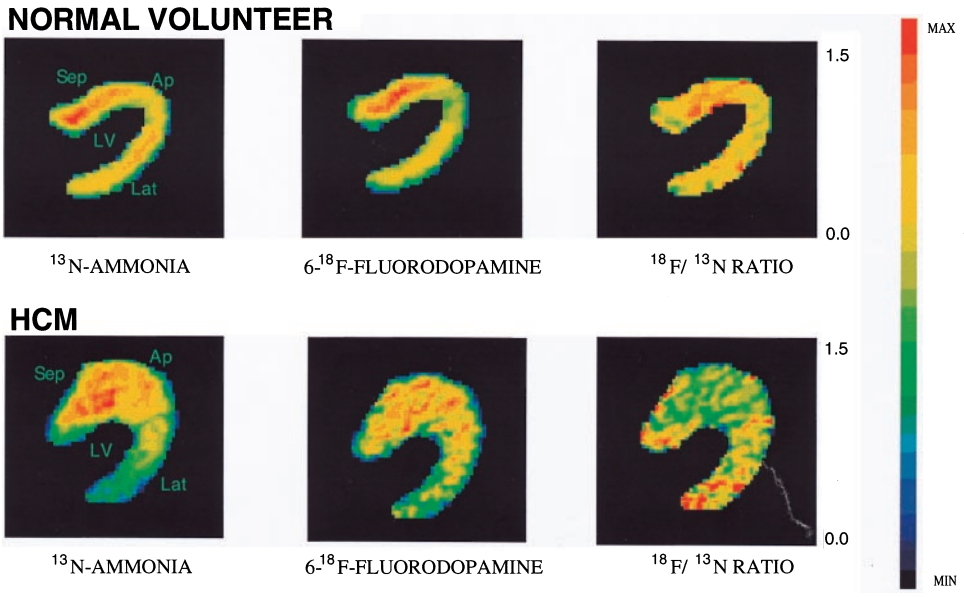

Figure 2. Thoracic positron emission tomographic scans depicting **(left)** myocardial ^{13}N-ammonia–derived radioactivity, **(middle)** 6-[^{18}F]-fluorodopamine–derived radioactivity, and **(right)** the ratio of ^{18}F:^{13}N in **(top)** a normal volunteer and **(bottom)** a patient with hypertrophic cardiomyopathy, after IV injection of 5 mCi ^{13}N-ammonia and then 1 mCi 6-[^{18}F]-fluorodopamine. Sep = septum; Lat = lateral wall; Ap = apex; LV = left ventricle.

Peak ^{18}F-FDA–derived radioactivity (9457 ± 1074 nCi · kg/cc · mCi in hypertrophied regions, 9436 ± 1084 nCi · kg/cc · mCi in nonhypertrophied regions) and mean values for k or y_o (Table 1) did not differ between hypertrophied and nonhypertrophied regions in patients with HCM.

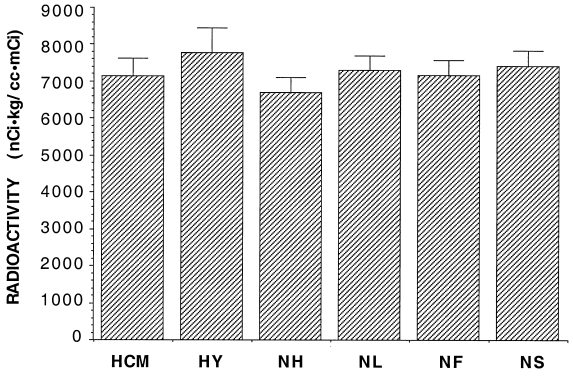

Figure 3. $^{13}NH_3$-Derived radioactivity in patients with hypertrophic cardiomyopathy and normal volunteers. HCM = average myocardial radioactivity of patients with hypertrophic cardiomyopathy (n = 8); HY = radioactivity in hypertrophied regions of patients with HCM (n = 8); NH = radioactivity in nonhypertrophied regions of patients with HCM (n = 5); NL = average radioactivity in left ventricular myocardium of normal volunteers (n = 15); NF = radioactivity in left ventricular free wall of normal volunteers (n = 15); NS = radioactivity in septum of normal volunteers (n = 15).

Hypertrophied regions in patients with HCM versus controls. After correction for the partial volume effect, $^{13}NH_3$-derived radioactivity in hypertrophied regions of patients with HCM (7767 ± 680 nCi · kg/cc · mCi) did not differ significantly from that in the left ventricular myocardium of normal volunteers (7428 ± 413 nCi · kg/cc · mCi; Fig. 3).

Neither mean peak ^{18}F-FDA–derived radioactivity nor $^{13}NH_3$-derived radioactivity (6694 ± 425 nCi · kg/cc · mCi) in nonhypertrophied regions of patients with HCM differed from the corresponding values in normal volunteers.

Perfusion-adjusted ^{18}F-FDA–derived radioactivity. In the hypertrophic regions of patients with HCM, the mean ratio of ^{18}F:^{13}N was significantly less than that in normal volunteers (F = 15.7, p = 0.001). The ^{18}F-FDA–derived radioactivity declined in a time-dependent manner (F = 137.4, p = 0.0001), and the groups differed significantly in the trends of ^{18}F:^{13}N (F = 3.20, p = 0.0005). The ratio of peak ^{18}F-FDA–derived radioactivity to $^{13}NH_3$-derived radioactivity was also significantly lower in hypertrophied than in nonhypertrophied regions of HCM patients (t = 2.13) or in normal volunteers (t = 3.87, p = 0.0005; Fig. 4). Among the five patients with asymmetric septal hypertrophy, the mean ratio of septal ^{18}F:^{13}N was also significantly less than that in normal volunteers (F = 13.4, p = 0.0023). The ^{18}F-FDA–derived radioactivity declined in a time-dependent manner (F = 115.8, p = 0.0001), and the groups differed significantly in the trends of ^{18}F:^{13}N (F = 3.27, p = 0.0005).

Table 1. Kinetic Parameters for 6-[^{18}F]-Fluorodopamine–Derived Radioactivity in Normal Volunteers and in Patients With Hypertrophic Cardiomyopathy

Parameter	Normal Volunteers	HCM		
		Mean LV	Hypertrophied Region	Nonhypertrophied Region
y_o Early	7146.44 ± 432.32	6959.49 ± 743.49	7361.33 ± 944.81	6943.02 ± 1325.70
y_o Late	5944.78 ± 616.09	4795.39 ± 665.87	5176.43 ± 563.19	4580.58 ± 663.42
k Early	0.0465 ± 0.0081	0.0427 ± 0.0039	0.0418 ± 0.0058	0.0525 ± 0.0068
k Late	0.0041 ± 0.0007	0.0053 ± 0.0009	0.0055 ± 0.0008	0.0050 ± 0.0004
$T_{1/2}$ early	14.91	16.24	16.58	13.20
$T_{1/2}$ late	169.86	130.05	126.33	137.50

Mean values are expressed as ± SEM. y_o = y-intercept; nCi · kg/cc · mCi; k = apparent rate constant, min^{-1}; $T_{1/2}$ = half time, min; HCM = hypertrophic cardiomyopathy; LV = left ventricular myocardium.

Peak ^{18}F-FDA–derived radioactivity correlated positively with $^{13}NH_3$-derived radioactivity across subjects (Fig. 5). For a given amount of $^{13}NH_3$-derived radioactivity, patients with HCM had lower values for peak ^{18}F-FDA–derived radioactivity in the hypertrophied than nonhypertrophied regions ($F = 12.7$, $p = 0.0044$) and myocardium of normal volunteers ($F = 16.2$, $p = 0.0006$). The relationship between ^{18}F-FDA–derived radioactivity and $^{13}NH_3$-derived radioactivity did not vary as a function of the diagnostic group or hypertrophied status. For a given amount of $^{13}NH_3$-derived radioactivity, peak ^{18}F-FDA–derived radioactivity in nonhypertrophied regions of patients with HCM was similar to that in normal volunteers.

DISCUSSION

The main finding of the present study was in patients with HCM, ratios of ^{18}F-FDA–derived radioactivity to $^{13}NH_3$-derived radioactivity in hypertrophied regions were significantly smaller than those in nonhypertrophied regions or in left ventricular myocardium of normal volunteers. As explained below, these findings indicate decreased neuronal uptake of ^{18}F-FDA by cardiac sympathetic nerve terminals for a given amount of delivery by blood perfusion in the hypertrophied regions.

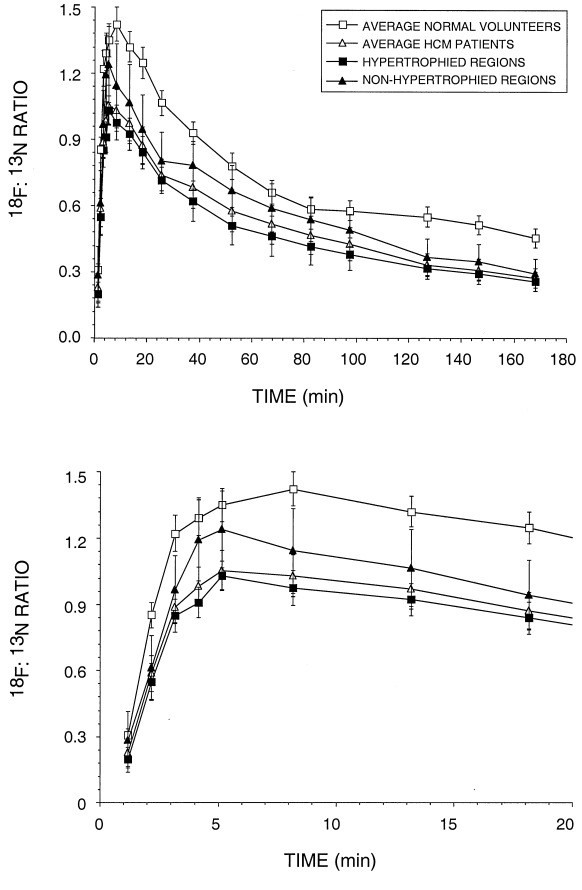

Figure 4. Mean values (±SEM) for the ratio of ^{18}F:^{13}N in septum or average of left ventricular myocardium of normal volunteers (n = 15) and in hypertrophied (n = 8) and nonhypertrophied regions (n = 5) of patients with hypertrophic cardiomyopathy, after injection of ^{13}N-ammonia and then 6-[^{18}F]-fluorodopamine.

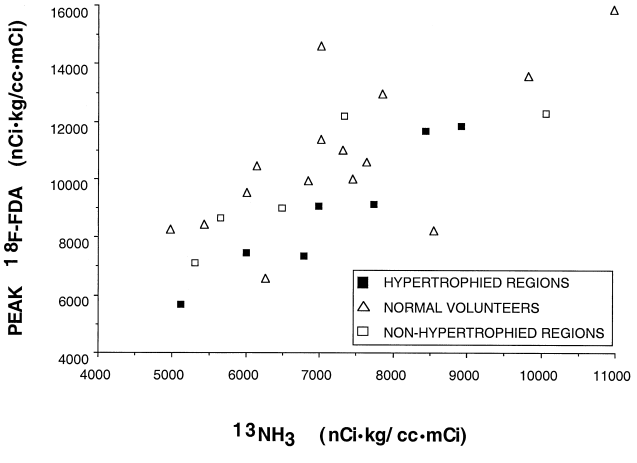

Figure 5. Relationship between peak ^{18}F-FDA–derived radioactivity and $^{13}NH_3$-derived radioactivity in hypertrophied and nonhypertrophied regions of 7 patients with HCM (another 1 outlier deleted) and in left ventricular myocardium of 15 normal volunteers.

Cardiac sympathetic function in hypertrophied regions. Shapes of curves relating myocardial ^{18}F-FDA–derived radioactivity with time in patients with HCM did not differ from those in normal volunteers, even after adjustment for perfusion. Thus, the decrease in perfusion-adjusted ^{18}F-FDA–derived radioactivity did not result from accelerated loss of ^{18}F-FDA–derived radioactivity after neuronal uptake of the tracer, as would occur with decreased efficiency of the vesicular monoamine transporter (25) or with increased regional sympathetic nerve traffic (32).

The present results confirm and extend those from other studies using different sympathoneural and perfusion imaging agents, indicating decreased Uptake-1 activity in myocardium of patients with HCM. Shimizu et al. (22) reported reduced ^{123}I-MIBG–derived radioactivity in hypertrophied regions of patients with HCM who had a conduction disturbance or decrease in or disappearance of a negative T wave during 12 months of serial electrocardiography, compared with patients who had an increase in or appearance of a negative T wave; however, the study did not include a control group and did not consider possible regional differences in perfusion.

In addition, Nakajima et al. (36) noted reduced ^{123}I-MIBG–derived radioactivity for a given amount of ^{201}Tl uptake in hypertrophied regions of patients with septal thicknesses exceeding 16 mm, compared to patients with septal thicknesses less than 16 mm; this study also did not include a control group. Schäfers et al. (23) found a decreased cardiac volume of distribution of ^{11}C-hydroxyephedrine in patients with HCM compared with values in control subjects, consistent with decreased neuronal uptake; however, that study did not examine possible regional localization of the abnormality within the myocardium. Ungerer et al. (21) reported a close correlation between ^{11}C-hydroxephedrine uptake and tissue norepinephrine content in cardiomyopathic human heart; however, the patients all had dilated, not hypertrophic, cardiomyopathy.

Decreased ^{18}F-FDA uptake in hypertrophied regions in patients with HCM could reflect relative sympathetic hypoinnervation, such as by "dilution" of nerve terminals by hypertrophied myocardial cells and interstitial fibrosis (4). Because myocardial uptake and retention of ^{18}F-FDA requires the energy-dependent Uptake-1 process (25), and because patients with HCM can have impaired oxidative and glucose metabolism in hypertrophied regions (37,38), locally decreased uptake of ^{18}F-FDA might also result from local metabolic changes. Although decreased neuronal uptake could also result from increased effective arteriovenous shunting, related to decreased arteriolar density (39), this would not have decreased the ^{18}F:^{13}N ratio.

Myocardial perfusion in hypertrophied regions. Available published reports about regional myocardial blood flow and perfusion in patients with HCM have been remarkably inconsistent. Investigators (36) reported increased regional uptake of ^{201}Tl in the hypertrophied septa of patients with HCM. Camici et al. (40) found more $^{13}NH_3$-derived radioactivity in the hypertrophied septum than in the nonhypertrophied free wall, although the difference from corresponding values in control subjects was not significant. In contrast, Ishiwata et al. (37) and Tadamura et al. (38) reported reduced ^{11}C-acetate–derived radioactivity, which is a measure of myocardial perfusion (41), and Grover-McKay et al. (34) and Nienaber et al. (42) reported reduced $^{13}NH_3$-derived radioactivity in the hypertrophied regions. Hypertrophied regions have normal uptake of ^{15}O-water (42–44).

Some of these differences may have arisen from lack of correction for the partial volume effect in hypertrophied myocardial regions. In the present study, after correction for the partial volume effect, $^{13}NH_3$-derived radioactivity in hypertrophied regions was approximately normal.

Cardiac sympathetic innervation and myocardial perfusion in nonhypertrophied regions. Both ^{18}F-FDA–derived and $^{13}NH_3$-derived radioactivity levels were normal in nonhypertrophied regions of patients with HCM, and trends in perfusion-adjusted ^{18}F-FDA–derived radioactivity were similar in patients with HCM and in normal volunteers. These findings indicate normal postganglionic nerve traffic to functionally intact sympathetic nerve terminals in the nonhypertrophied regions.

In summary, decreased perfusion-adjusted ^{18}F-FDA–derived radioactivity appears to reflect decreased neuronal uptake (Uptake-1) by sympathetic nerves in hypertrophied but not in nonhypertrophied regions of patients with HCM. Because of the importance of Uptake-1 for terminating the actions of catecholamines in the human heart (19), decreased Uptake-1 activity would be expected to augment delivery of locally released and circulating catecholamines to adrenoceptors in the hypertrophied myocardium during sympathetic or adrenomedullary activation. This in turn could contribute to hypercontractility, susceptibility to ventricular arrhythmias, reduced coronary vasodilator reserve, and progressive hypertrophy in HCM.

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